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Commentary

Harnessing Neuroimaging Capability in Pediatric Stroke: Proceedings of the Stroke Imaging Laboratory for Children Workshop



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ABSTRACT

On June 5, 2015 the International Pediatric Stroke Study and the Stroke Imaging Laboratory for Children cohosted a unique workshop focused on developing neuroimaging research in pediatric stroke. Pediatric neurologists, neuroradiologists, interventional neuroradiologists, physicists, nurse practitioners, neuropsychologists, and imaging research scientists from around the world attended this one-day meeting. Our objectives were to (1) establish a group of experts to collaborate in advancing pediatric neuroimaging for stroke, (2) develop consensus clinical and research magnetic resonance imaging protocols for pediatric stroke patients, and (3) develop imaging-based research strategies in pediatric ischemic stroke. This article provides a summary of the meeting proceedings focusing on identified challenges and solutions and outcomes from the meeting. Further details on the workshop contents and outcomes are provided in three additional articles in the current issue of Pediatric Neurology.

Keywords: pediatric, stroke, neuroimaging, MRI, diffusion, perfusion, cerebrovascular reactivity

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Introduction

Pediatric arterial ischemic stroke (AIS), defined by focal infarction within a vascular territory, occurs in one in 3500 live births and 1 to 3 per 100,000 children per year.^{1,2} Pediatric AIS remains one of the top ten causes of death

and lifelong disability in childhood. The socioeconomic impact of pediatric stroke is significant.^{3–5}

Brain injury because of AIS results from arterial occlusion, critical decrease in regional perfusion, and focal brain tissue ischemia. Within the focal ischemic zone complex molecular and tissue changes occur. After acute ischemic infarction, at least some functional recovery occurs related to compensatory brain rewiring and repair. Characterization of these mechanisms from infancy to adult years is an important area of research. Emerging research-based imaging techniques can further expand our understanding of the mechanisms underlying focal ischemic injury and repair within the developing brain. An enhanced understanding of these mechanisms will ultimately help us to develop novel treatment approaches aimed at minimizing injury and enhancing mechanisms of repair, thereby improving outcomes in pediatric AIS (Table).

Although similar clinical challenges (timely detection and targeted therapy) exist in AIS across pediatric and adult patients, differences in mechanisms of stroke pathogenesis, injury, and repair likely exist. Clinical management relies upon appropriate neuroimaging to provide specific diagnosis, etiological classification, and patient selection for possible therapies. Yet imaging strategies that are feasible in adults present specific challenges in infants and children. This workshop was convened to harness opportunities for developing systematic and collaborative research to address the unique aspects of imaging in the pediatric stroke population.

The Stroke Imaging Laboratory for Children (SILC) cohosted the meeting in collaboration with the International Pediatric Stroke Study.⁶ SILC was recently established at the Hospital for Sick Children Research Institute to advance imaging research in pediatric stroke. Leveraging the latest imaging technology, SILC aims to employ synergistic

TABLE.
Imaging Stroke Mechanisms

Cerebral Artery Wall Pathology	Wall Imaging MRI
Cerebral artery lumen (e.g., occlusion)	MRA
Perfusion drop	Perfusion imaging, CVR, SWI
Brain tissue cell death	DWI, DKI
Recanalization	MRA
Reperfusion	Perfusion imaging, CVR
Blood-brain barrier breakdown	Gadolinium enhancement
Hemorrhagic conversion of bland infarct	SWI
Neuronal salvage	??
Reperfusion injury	DCE
Plasticity and repair	fMRI, MEG
Rewiring	DTI

Abbreviations:
CVR = Cerebrovascular reactivity
DCE = Dynamic contrast enhancement
DKI = Diffusion kurtosis imaging
DTI = Diffusion tensor imaging
DWI = Diffusion-weighted imaging
fMRI = Functional magnetic resonance imaging
MEG = Magnetoencephalography
MRA = Magnetic resonance angiogram
MRI = Magnetic resonance imaging
SWI = Susceptibility-weighted imaging
?? = Requires further research

neuroimaging techniques to provide new insights into pediatric stroke. Consistent with these aims, Part I of the workshop consisted of slide presentations that emphasized (1) acute practical imaging needs and solutions; (2) imaging of acute pathogenesis; (3) stroke lesion delineation; (4) imaging stroke impact: recovery and plasticity; and (5) building a collaborative network. Part II of the day consisted of breakout sessions with working groups focused on three main objectives: (1) establishing a group of experts to collaborate in advancing imaging; (2) developing consensus-based clinical and research magnetic resonance imaging (MRI) protocols; and (3) developing and sharing imaging-based research strategies in pediatric AIS. A major outcome of the workshop was the development of four complementary articles designed to address the aforementioned objectives. The current article presents the overview of the meeting and the framework from which the other more specific articles were developed.^{7–10}

Pediatric stroke: Overview, clinical challenges, and imaging solutions

Part I of the day consisted of presentations that outlined the challenges and potential imaging solutions to timely diagnosis, treatment selection, and recognition of the pathogenesis of pediatric AIS in the acute setting.

Imaging for stroke diagnosis—the acute infarct and penumbra

The differential diagnosis of acute onset focal neurological symptoms in childhood is broad, posing a challenge to accurate and timely diagnosis of pediatric AIS.^{11,12} Specific imaging confirmation of stroke is necessary. In adults, the differential diagnosis of acute focal deficits is narrow and cranial computed tomography (CT) imaging to rule out bleeding is the standard initial imaging modality. However, CT has limited sensitivity for pediatric AIS, missing 50% to 80% of lesions verified by MRI.¹³ Exposure to ionizing radiation is an additional consideration in the developing brain.¹⁴ Accordingly, MRI has emerged as the modality of choice for the initial diagnosis of pediatric AIS. Diffusion-weighted imaging (DWI) utilizes the diffusion properties of water to interrogate cellular integrity and injury.^{15,16} Animal and human studies have shown that ischemic injury and restricted diffusion become evident on diffusion-weighted MRI when cerebral blood flow (CBF) falls below 20 mL per 100 g/minute. Thus diffusion restriction on MRI in pediatric AIS is meant to represent irreversibly infarcted tissue or the ischemic core. Outside the ischemic core, where CBF reduction may not have reached this critical threshold, DWI remains normal but perfusion-weighted imaging (PWI) is abnormal. This finding is the neuroimaging equivalent of the penumbra, which is potentially viable, but vulnerable tissue that may provide a therapeutic target for recanalization and neuroprotective care in acute ischemic stroke.^{17,18}

Identification of patients most likely to benefit from recanalization and neuroprotection care requires perfusion imaging. The main MR perfusion techniques used in adults, including T2* dynamic susceptibility contrast imaging and T1 dynamic contrast enhancement, require the use of gadolinium contrast agents. The invasive nature of the contrast

administration (high volume bolus in small venous channels), risk of anaphylaxis, nephrotoxicity, slow clearance and, in the case of repeated administrations, retention of gadolinium contrast in the brain^{19–21} pose significant challenges to their application in the pediatric population.

Dr. A. Vossough and Dr. M. Rivkin presented new opportunities of assessing brain perfusion in the pediatric stroke population as follows:

- (1) Arterial spin labeling (ASL) perfusion harnesses the properties of blood water protons to provide an endogenous contrast agent. Clinically available commercial ASL sequences are not yet validated in childhood as a result of the technical challenges of studying steno-occlusive disease in this developmentally heterogeneous group. However, ASL offers significant promise for improving our understanding and treatment of acute pediatric stroke and has recently been successfully used in children with moyamoya.^{10,22}
- (2) High-spatial-resolution three-dimensional gradient echo (GRE) MR sequence using susceptibility-weighted imaging (SWI) is another promising approach to measure perfusion. This sequence has been used in healthy and asphyxiated newborns,²³ and recently, for assessing penumbra, in neonates with stroke.²⁴ In AIS, severe reduction of cerebral perfusion is associated with an increased deoxyhemoglobin-to-oxyhemoglobin ratio because of a compensatory increase in the oxygen extraction fraction.²⁵ Regional variations in the SWI appearance of hypointense veins draining ischemic brain (with higher concentration of deoxyhemoglobin) and normally perfused brain (with lower concentration of deoxyhemoglobin) have been demonstrated in adults^{26–28} and children^{29,30} with AIS. Further exploration of this modality in the pediatric population is required.^{8,9}

Imaging assessment for directing hyperacute and acute therapies

Dr. Catherine Amlie-Lefond presented on how imaging can inform patient selection for hyperacute reperfusion therapies and highlighted important imaging outcomes. Reperfusion therapies, with endovascular devices and thrombolytic agents, are the mainstay of treatment for selected, eligible adult patients treated within 6 hours from onset of AIS. Animal studies of cell death, apoptosis, and autophagy demonstrate age-related similarities and differences in vulnerability and resilience to ischemic injury.^{31,32} These findings emphasize the opportunity for reperfusion and neuroprotection in pediatric AIS. However, the absence of safety data with endovascular devices presents a significant barrier to their use in young children with AIS stroke.^{31,33}

One complication of thrombolysis is hemorrhagic transformation of the ischemic infarct, with an associated increased likelihood of severe neurological deficit and poor outcome in children.^{34,35} The use of MR imaging data to aid patient selection for thrombolysis has been associated with improved outcomes and reduced risks from acute thrombolysis in adults. A number of these approaches, relevant to the pediatric population, were presented in the workshop:

- (1) Large volume (more than 2/3 of the middle cerebral artery territory) infarcts are associated with an increased risk of hemorrhagic transformation. Hence, rapid determination of the acute lesion volume is desirable. Simple visual assessment of infarct volume is feasible using the Alberta Stroke Program Early Computed Tomographic scoring method,³⁶ which predicts functional outcome and hemorrhage risk in patients who are candidates for intravenous thrombolysis. The scoring system has subsequently been applied to pediatric AIS and to MRI.^{36–38} Drs. T. Schmah and R. Filippi presented novel and validated semiautomated volumetric tools for potential future application to children. However, recognized limitations include lesion segmentation and the need to preset apparent diffusion coefficient values, the latter being more problematic in the setting of pediatric acute ischemic stroke.³⁸
- (2) Large baseline PWI lesion volumes, known as “malignant” low perfusion patterns (PWI [Tmax greater than 8 seconds] volume of more than 85 mL as the optimal definition of the malignant profile), are associated with higher rates of thrombolysis-related parenchymal hemorrhage and severe disability or death.³⁹ In comparison, reperfusion therapy in patients with “target” mismatch patterns has significantly favorable clinical outcomes.^{40,41} Therefore characterization of pediatric PWI/DWI patterns could improve the selection of ideal pediatric AIS candidates for future trials of recanalization treatments.
- (3) Dr. N. Dlamini presented on MR-based qualitative and quantitative methods of assessing cerebrovascular reactivity (CVR) using clinically available T2* gradient echo sequences. The brain relies on autoregulation as an important mechanism for maintaining CBF despite variations in systemic blood pressure. CVR compares cerebral tissue perfusion at baseline and during hypercapnic challenge to evaluate regional cerebral autoregulation. CVR is an important marker of cerebrovascular reserve that has been shown to predict ischemic risk in adults.^{42,43} Studies of CVR in the acute and chronic phases after stroke can provide information regarding failure of regional and global autoregulatory capacity and individual patient susceptibility to ischemic injury, supporting patient selection for acute and subacute reperfusion strategies. The CVR technique has been validated in both adult and pediatric populations and provides a novel opportunity for adoption into clinical practice.^{44–46}
- (4) Dr. A. Kassner described the benefits of blood-brain barrier (BBB) imaging in stroke. Adult imaging studies of BBB integrity have demonstrated an association between BBB disruption and an increased risk of hemorrhagic transformation.⁴⁷ Recombinant tissue plasminogen activator (tPA) itself further compromises BBB integrity, potentially contributing to increased hemorrhagic transformation and adverse patient outcomes.⁴⁸ No longitudinal data exist on BBB permeability changes from the first few hours to the first days after acute ischemic stroke.^{48,49} Animal studies have identified imatinib as a potential neuroprotective agent to preserve the BBB after acute ischemic stroke, which could result in the extension of the therapeutic window in pediatric stroke.^{10,50}

Imaging for stroke etiology and classification

Determining the etiology of stroke in childhood is a major challenge. Classification systems have been developed to better predict risk and recurrence, as well as guide management.⁵¹ All of these systems are highly dependent on the nature and quality of the clinical information in addition to brain and vascular imaging.^{52–54}

Intracranial arteriopathy is the leading cause of pediatric AIS and confers a fivefold increase in stroke recurrence risk.^{55,56} Transient cerebral arteriopathy, intracranial arterial dissection, and moyamoya represent the common arteriopathies of childhood, which typically involve the arteries of the internal carotid bifurcation. Available luminal MR or CT angiography techniques are unable to reliably distinguish across arteriopathy subtypes. Dr. D Mikulis shared his experience of vessel wall imaging (VWI) using high-resolution 3 Tesla MRI with gadolinium in adults. VWI has been shown to differentiate various arterial pathologies, through distinct patterns of contrast enhancement.^{57,58} However, the few available reports in children are limited to case studies. The use of contrast and the interpretation of vessel wall contrast enhancement remain as challenges to the implementation of contrast-based VWI in childhood.⁵⁹ Further exploration of noncontrast and nonenhanced wall imaging is required.⁶⁰ Simple angiographic patterns of arterial anatomy, such as arterial tortuosity, may also provide clues to the nature of arteriopathic stroke in childhood.^{61,62}

Imaging impact of stroke and plasticity

In the final presentations of Part I, we explored imaging predictors of outcome, recovery, and plasticity described in the following sections.

Imaging predictors of outcome

In children with AIS, sensorimotor and cognitive outcomes vary widely and this variability remains relatively unexplained. Kirton et al. previously reported on a qualitative approach to the classification of presumed perinatal ischemic stroke based on visually matching the infarct distribution to known vascular territories. They demonstrated the ability of the classification system to predict outcome.⁶³ Infarct volume is another imaging biomarker of outcome.⁶⁴ However, the measurement of chronic infarct volumes is technically challenging and time consuming given the need for manual segmentation. Dr. N. Stence et al. reported on an exploratory method of estimating volume of perinatal AIS on chronic imaging that can compensate for the changes in brain volume in early infancy. The technique compares healthy ipsilesional versus contralesional hemispheric tissue volumes using manual segmentation methods. They demonstrated that this indirect method accurately estimates perinatal infarct volumes more accurately than direct methods.⁶⁵

Automated methods exist that allow for lesion classification, volume assessment, tracking of longitudinal change, and potentially automatic prediction of outcome in children and neonates with AIS and other brain lesions.^{66–68} However, few have been systematically studied in the pediatric population. Dr. R. Filippi presented a novel computer

assisted volumetric method, which markedly simplifies automated volume measurement of stroke lesions, and has been developed and validated with clinical outcome severity in pediatric acute infarcts.⁶⁹ Additional improvements in automated stroke lesion detection and measurement will be realized with better methods of registration and segmentation of brain lesions.

Dr. A. Kirton presented on clinically relevant imaging biomarkers in brain locations remote from the stroke lesion. Diaschisis is a term used to describe the focal depression of neurological function in a brain region that is distant from the original site of injury but anatomically connected to it by fiber tracts.^{70,71} Ipsilesional acute Wallerian degeneration (also termed “preWallerian degeneration”) appearing as restricted diffusion MRI signal within descending corticospinal tracts has been correlated with chronic motor deficits in neonatal,^{72–74} childhood,^{75,76} and adult stroke.^{77–81} Subtle coexisting restricted diffusion has also been noted in the contralesional corticospinal tract within the pons.⁷⁵ However, the pathological basis and significance of the latter finding is yet unknown.⁷⁶ Such early outcome predictors may inform stroke recovery mechanisms and aid in patient selection for clinical trials.

Imaging of stroke recovery and plasticity

Understanding the basis of neuroplasticity and after stroke sensorimotor recovery can help inform prognosis, rehabilitation therapies, and future trials in the chronic phase of pediatric acute ischemic stroke. Neuroplasticity refers to the ability of the brain to respond and modify its structure and function after injury. Concepts of “young age plasticity advantage” or the “Kennard-effect”^{82–84} versus “early vulnerability”⁸⁵ have recently merged into the concept of a recovery continuum across maturation between plasticity and vulnerability in pediatric acute ischemic stroke.⁸⁶ Several conventional and novel neuroimaging techniques can interrogate the underlying plasticity processes, such as MR diffusion techniques and functional MRI.

MR diffusion techniques allow for the assessment of tissue microstructure integrity. MR-based diffusion tensor imaging (DTI) allows for the assessment of white matter microstructure integrity and tractography. DTI studies in children with perinatal and childhood ischemic stroke have demonstrated a relationship between lower fractional anisotropy values and poor motor outcome in children highlighting the structure-function relationship in this group.^{87,88}

Alternative diffusion imaging approaches and models, including intravoxel incoherent motion (IVIM) and multi-shell high angular resolution diffusion imaging⁸⁹ coupled with multicompartiment models (e.g., neurite orientation dispersion and density imaging (NODDI)) have also shown promise for the assessment of acute stroke. Such approaches make it possible to assess fiber orientation and both intracellular and free water diffusion in a single voxel. Preliminary work in adult stroke patients suggests that NODDI metrics may detect changes in stroke regions not otherwise detectable using traditional diffusion imaging approaches.⁹⁰

The application of functional MRI (fMRI) and magnetoencephalography (MEG) imaging techniques to inform our understanding of recovery and plasticity after stroke in

childhood was summarized in presentations by Dr. T. Domi and Dr. D. Cheyne, respectively. Functional MRI measures the regional blood oxygen level—dependent (BOLD) signal as an indirect measure of regional neuronal activity. fMRI compares different brain regions at rest—resting state fMRI—or during a task—task-based fMRI. Resting state fMRI is able to provide detailed spatial information about the baseline extent of neuronal activity within cerebral networks by measuring the coherent fluctuations of fMRI signals (functional connectivity).⁹¹ Adult stroke studies have reported on the predictive value of fMRI in evaluating altered ipsilesional and contralesional brain network integrity underlying clinical motor and cognitive deficits.^{92,93} Studies of network reorganization in children after stroke are few.^{94,95} However, studies using fMRI to evaluate hand function in children with remote stroke by Domi et al.⁹⁶ demonstrated a high correlation between motor deficit and greater asymmetry in fMRI activations. Differences in sensorimotor reorganization after ischemic injury may impact neuroplasticity and response to rehabilitative interventions.^{97,98}

Although fMRI is unable to provide direct information about network activity, other electrophysiologic measures can do so. Transcranial magnetic stimulation can provide information about activation remapping of the sensorimotor cortex after a lesion and has been used in pediatric stroke. However, spatial information is limited.^{99,100} MEG can be used to detect cortical oscillatory activity and can localize frequency specific brain activity with high temporal and spatial resolution providing information about neural network reorganization, plasticity, and repair after stroke. Perilesional, ipsilesional, and contralesional alterations in frequency and amplitude of sensorimotor cortical excitability correlate with clinical outcome in adult stroke.^{101,102} Multimodal imaging studies have demonstrated bilateral alterations in somatosensory evoked fields in children with hemiplegic cerebral palsy^{103,104} and disruption of thalamocortical projections.¹⁰⁵ Studies using MEG in this population have shown modulated somatosensory evoked fields in the affected hemisphere after cast-therapy intervention¹⁰⁶ and Juenger et al.⁹⁷ demonstrated differential neuroplasticity and outcomes in children with stroke after constraint-induced movement therapy. MEG studies examining abnormal cortical excitability and short-term plasticity in the somatosensory system in children with after stroke dystonia are ongoing.

Building collaborative networks

The International Pediatric Stroke Study (IPSS) arose from the need to establish a large collaborative community of experts with an interest in pediatric stroke.¹⁰⁷ To date, the IPSS accounts for 57 active centers (total 219 since 2003) and more than 5000 infants and children with ischemic stroke are enrolled in the primary IPSS study. The IPSS has generated 18 clinical and epidemiologic peer-reviewed articles to date, which have highlighted the range of challenges in diagnosis and management, and the need for further systematic research including treatment trials. Several IPSS substudies funded by the National Institute of Neurological Disorders and Stroke and other agencies are ongoing.

The “Vascular Effects of Infection in Pediatric Stroke”¹⁰⁸ study used the IPSS network to enroll more than 350 children with AIS and age-matched controls, collecting all clinically obtained brain and vascular imaging on more than 300 stroke cases from 22 centers. Central storage, classification, and imaging review at University of California, San Francisco has enabled more accurate classification of stroke etiology and arteriopathy subtypes.¹⁰⁸ In addition, the resultant imaging library became a valuable resource, allowing new analytic techniques to be retrospectively applied, such as a method for measuring arterial tortuosity using MRA data.⁶¹ However, imaging data in vascular effects of infection in pediatric stroke (VIPS) study were limited by variability in the clinical stroke imaging protocols at the 37 different enrolling sites.

Multicenter imaging collaborations and future trials present additional challenges beyond dealing with large databases of imaging studies. They include the need for a quality assurance process to ensure anonymization of the data and an appropriate bioinformatics infrastructure with support to electronically transfer, store, and analyze multidimensional data. The varying imaging software and technology can also pose challenges to multicenter imaging and data analysis. Biological samples for genomic and proteomic analysis can provide additional relevant data in pediatric AIS research potentially correlating with imaging markers of mechanisms of injury and recovery. Essential to the highly collaborative network is the domain expertise of the various teams in software systems and programming, mathematics and statistics, neuroscience, and medicine. The development of integrated neuroinformatics for translation research relies heavily on the neuroimaging workflow pathways with the potential to use multitier preprocessing pipelines for image review, interpretation, and analysis. Alternatively, data-driven approaches using a neuroinformatics systems approach to big data analysis do not require understanding of mechanisms and can be used to augment clinical decision making. Finally, building a collaborative network also relies on policies designed to both safeguard privacy and security and to define how data ownership and access will be managed and reflected in authorship. Both are necessary conditions for potential contributors to be comfortable sharing their data.

There are many recent examples of consortia that have tackled these issues in specific disease domains. Such examples often come with extensive documentation, infrastructure, and associated open source software. Beyond Vascular Effects of Infection in Pediatric Stroke, other relevant consortia include the Biomedical Informatics Network (BIRN) and their approach to multisite neuroimaging studies (<http://www.birncommunity.org/>); different database approaches considered for adult stroke by the Canadian Centre for Stroke Recovery; and for multiple disease domains and data modalities, development of the Brain-CODE data repository and related governance structures by the Ontario Brain Institute. IPSS and SILC imaging repositories and other multicenter imaging collaborations will need to carefully assess such relevant prior experience and available infrastructure as they develop.

Breakout Sessions

Part II of the day consisted of breakout sessions with working groups focused on the three aforementioned main

objectives: (1) establishing a group of experts to collaborate in advancing imaging; (2) developing consensus-based clinical and research MRI protocols; and (3) developing and sharing imaging-based research strategies in pediatric AIS.

Since this first meeting, the group met at the American Society for Neuroradiology 54th Annual Meeting, further solidifying the collaborative network initiated at the initial workshop and formalizing linkages within the IPSS Neuroimaging Subgroup. The immediate common goal of the IPSS and SILC laboratory was to develop standardized imaging protocols so that clinically obtained studies could be more readily compared across institutions. Hence, the publication of the two clinical guidelines in this issue^{8,9} and the research imaging article¹⁰ pursuant to the initial meeting is an important first step toward this goal. Finally, Brain Canada recently funded a platform support grant titled “Canadian Paediatric Stroke Imaging Research Platform: Harnessing an International Focus” based at SILC to pilot a prospective imaging study across an initial five pilot sites with a view to further expansion of multisite prospective research imaging in the next phase. The initial study will enroll 90 children with acute AIS. Participants will be imaged with many of the research techniques described previously during acute, subacute (three months), and chronic (12 months) phases. SILC will serve as a hub for imaging data and grant operations.

Conclusions and next steps

We report the proceedings of the first cohorted IPSS and SILC workshop focused on developing neuroimaging research in pediatric stroke. We brought together a group of experts who during the course of the day highlighted the challenges of diagnosis and management of pediatric AIS, and the opportunities to address these challenges using conventional and novel imaging techniques. Including this, four articles will be published as a result of the proceedings of this workshop, and the research imaging collaborative network established.

Large multicenter research networks, which include the IPSS are now well-established and provide the foundation for fostering neuroradiologists, stroke neurologists, and imaging scientists to collaborate and add multiple dimensions to the existing data repository, including imaging. Such infrastructure and collaborations will improve the clinical care of pediatric stroke through the creation of consensus-based imaging protocols and hypothesis-driven research protocols to further elucidate the pathophysiology and mechanisms of focal injury and recovery in the developing brain.

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